

REMARKS

Claim 1 has been amended to affirmatively state that the claims only include those compounds that have p38 α inhibiting activity and to define Z³ as N in accordance with the election. Claim 17 has been amended to delete compounds that the Office has pointed out are not included in within the scope of the generic compound of claim 1, and new claim 34 includes such compounds. No new matter has been added and entry of the amendment is respectfully requested.

Restriction Requirement

Applicants gratefully acknowledge that the Office will examine all of the method claims where Z³ is N, *i.e.*, the claims of Groups I-III and the portion of Group IV where Z³ is not CR².

The Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1, 8-10, 13, 15 and 23 under 35 U.S.C. § 112, first paragraph (scope) is traversed and reconsideration is respectfully requested. First, the claims have been amended such that only compounds that inhibit p38 α are included within the scope of the claim.

In the second paragraph on page 4 of the action, the Office appears to suggest that each of the compounds must be tested, presumably to show efficacy. In support of this assertion, the Examiner relies on a 30-year-old Court of Customs and Patent Appeals case, *In re Fouche*. However, the issue in this case does not appear to be germane to the present application. The issue in the Fouche case is “whether appellants has provided *any* teaching of how to use compounds containing the heterocyclic members of the Markush group.” *See Fouche*, page 434, left column, last sentence of second full paragraph. The Court agreed that if the claimed compositions had “*some* therapeutic utility,” this rejection would have been overcome. *See*

Fouche, page 434, right column, first sentence of fourth full paragraph. However, although urged by the appellants, the record did not support such and thus the Court was forced to affirm the Board's decision. In contrast, the present application discloses "some therapeutic utility," namely, the therapeutic utility relating to the inhibition of p38 α kinase. Thus, according to the Court's suggestion in *Fouche*, this objection should be overcome. Moreover, the claims have been further amended to make it clear that only those compounds that inhibit p38 α kinase are included in the scope of the claims.

Similarly, in the earlier *Surrey* case, the Court said,

We find no unequivocal statement in appellant's specification or in his brief that compounds other than those actually tested are anticonvulsants or psychomotor stimulants. Applicant simply says *the "physical embodiments"* of the invention "have been tested...and found to possess" the named properties.

These facts are in contrast to the present application where applicants state on page 4, line 6, "Compounds of the invention have been found to inhibit p38 kinase, the α isoform in particular and/or TGF β " and then goes on to provide the generic formula. Further, on page 5, the application unequivocally states that "The compounds of formula 1 are useful in treating conditions which are characterized by overactivity of p38 kinase, in particular the α isoform and/or overactivity of TGF β ." There is no equivocation here. Thus, neither *Fouche* nor *Surrey* is on point.

Furthermore, experimentation would be only routine to determine whether compounds will inhibit p38 α kinase. A substantial number of the compounds as described will have such activity and any compounds that might not have such activity would not be difficult to eliminate by appropriate screens such as the one described in Example 7 of the present specification or others that are known to a skilled artisan. With regard to the Office's assertion that "No reasonable assurance have been made that the instant compounds as an entire class have the

required activities needed to practice the invention”, the applicants have amended the claims so only those compounds which inhibit p38 α kinase are included within the scope of the claims as mentioned above.

Second, applicants have not been provided any rationale or evidence that one of ordinary skill in the art would doubt that the guidance in the specification would enable practice of the full scope of the claimed invention without undue experimentation. Respectfully, applicants believe that the burden of proof has been unfairly shifted to them. As the Office is well aware, statements made in the specification are to be taken at face value unless there is a reason to doubt their veracity. *In re Marzocchi*, 439 F2d 220, 169 USPQ 367 (CCPA 1971). No explanation has been given as to why the specification fails to provide adequate guidance to allow the skilled artisan to make compounds having p38 α kinase activity.

Accordingly, it is believed this basis for rejection may be withdrawn.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1, 8-10, 13, 15, and 17 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite is traversed and reconsideration is respectfully requested.

With respect to the phrases “substituted or unsubstituted” or “optionally substituted with 1-3 substituents,” these phrases are used in the claims of issued U.S. Patent No. 6,476,031 and thus it is respectfully submitted that a skilled artisan would understand the meaning of these phrases. Further, claims in issued patents are presumptively definite and since the language in both the present sets of claims and the issued claims are so similar, the present claims should likewise be viewed as definite.

With regard to the terms “cyclicaliphatic” and “heteroaliphatic” and the definition of Ar, the Office asserts that these terms are unclear with respect to “the array of heteroatoms, size of

the rings, as well as nature of atoms as ring members.” In support of this assertion, the Office cites a 30 year old Court of Customs and Patent Appeals case, *In re Wiggins*, that defined heterocyclic “so broad that it does not even require that the heterocyclic group contain a carbon atom.” In contrast to the facts in that case, the cyclicaliphatic and heteroaliphatic nature of these substituents are readily understood by one having ordinary skill in the art. With regard to the nature of atoms as ring members, one skilled in the art would understand that aliphatic means related to an organic compound such as alkane or alkane substituents as suggested by the definition attached herewith. Thus, the nature of atoms and the ring members are carbon and hydrogen. Further, the present description on page 6, lines 19-20 is consistent with this definition and describes an aliphatic residue as being a hydrocarbyl residue that contains carbon and hydrogen. Similarly, the nature of the atoms of a heteroaliphatic moiety is similarly understood with respect to the carbon and hydrogen makeup, but also include a heteroatom as described on page 6, lines 19-25 of the present specification. Examples of heteroatoms are found on page 7, line 9, although a skilled person would understand that a heteroatom is an atom other than carbon in a ring of a heterocyclic compound, as defined in the attached Merriam-Webster definition attached herewith. In contrast to *Wiggins*, cited by the Office, the application in question did not even require that the heterocyclic group contain a carbon atom as described above and thus, the facts in that case do not apply to the present claims, where such a requirement is made. Thus, it is respectfully submitted that these terms are definite and readily understood by one of ordinary skill in the art. Nonetheless, claim 1 has been amended to define the “cyclicaliphatic” as a “cyclic hydrocarbyl aliphatic” and to similarly redefine “cyclic hetero aliphatic” without altering the claim scope.

With regard to items 3-6 in the action, the compounds at issue in claim 17 have been included in new claim 34. Thus, the rejection with respect to these claims is rendered moot.

With regard to item 7 on page 6 of the Office action, the Office objects to the terms “alkyl”, “arylalkyl” and “alkenyl”, allegedly based on “scope.” However, it is well settled that scope is not an issue relating to 35 U.S.C. § 112, second paragraph. Please see, MPEP § 2173.04, BREADTH IS NOT INDEFINITENESS, that states “If the scope of the subject matter embraced by the claims is clear and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. § 112, second paragraph.” In support of the Office’s assertion, a 30-year-old Court of Customs and Patent Appeals case, *In re Hawkins*, is cited; however, this case does not discuss indefiniteness is therefore irrelevant to the present rejection.

Furthermore, it is respectfully submitted that a skilled person would understand the meaning of alkyl, arylalkyl and alkenyl especially in view of the definitions set forth in pages 6-7 of the present application. Moreover, these identical terms are used in issued U.S. Patent No. 6,476,031, which are presumptively definite and thus the present claims should likewise be viewed as definite.

Therefore, it is respectfully submitted that all of the objections raised by the Office have been addressed and withdrawal of these rejections is respectfully requested.

The Art Rejections

The rejections under 35 U.S.C. § 102(a) of claims 1 and 8-10 as being anticipated by Alvi (Chem Abstracts) deLaszlo, and Anantanarayan (Chem Abstracts) are traversed and reconsideration is respectfully requested. Each of the references discloses a hetero cycle having a position corresponding to Z³ as CH and not N in accordance with the elected invention. The

claims have been amended so that the elected invention is reflected, namely, Z^3 is defined as being N.

Therefore, withdrawal of these rejections is respectfully requested.

The rejections of claims 1 and 8-10 under 35 U.S.C. § 103(a) as being allegedly obvious over a) Alvi (WO 99/18942) and b) Anantanarayan (WO 98/52940) are traversed and reconsideration is respectfully requested. The publication date on the Alvi document is April 1999 and on the Anantanarayan document is November 1998. These dates are subsequent to the date which applicants are entitled for priority, *i.e.*, 28 August 1998. According to the second paragraph of the examination guidelines for 35 U.S.C. § 102(e), WIPO publications of international applications are governed by the Code as amended by the American Inventors Protections Act of 1999 and the Intellectual Property and High Technical Amendments Act of 2002 only if such publications were the result of an international application filed before November 29, 2000 references. These applications were filed before such date.

According to the guidelines, such publications “have prior art effect under § 102(a) or (b) as of their publication date.” As the present application was filed before the publication date of either cited references, it is respectfully submitted that these rejections were made in error. It is respectfully requested that this rejection be withdrawn. If the Examiner is not convinced by these arguments the Examiner is kindly requested to further explain why these documents are available as references against the present claims.

Double Patenting Rejections

1. Statutory Double Patenting

The rejections of claims 16, and 24 under 35 U.S.C. § 101 as claiming the same invention as that of claims 6 and 9 of prior U.S. Patent No. 6,476,031 is traversed and

reconsideration is respectfully requested. The claims in the patent are directed to a method to inhibit p38 α and/or TGF- β activity comprising contacting the p38- α and/or TGF- β with a particular compound. In contrast, the present claims are directed to a method of inhibiting p38 α activity comprising contacting p38 α with a particular compound. As the claims in the present case are not identical to the claims in U.S. Patent No. 6,476,031, it is respectfully submitted that the statutory double patenting rejection has been made in error. As such, the withdrawal of this rejection is respectfully requested.

2. Obviousness Type Double Patenting

With respect to the rejection of claims 1, 8-10, 13, 15, 17, and 23 under the judicially created Doctrine of Obviousness-Type Double Patenting over claims 1-9 of U.S. Patent No. 6,476,031 and claims 1-8 of U.S. Patent No. 6,184,226, a terminal disclaimer over the application that issued into Patent No. 6,476,031 was filed on October 5, 2001, and, in addition, a terminal disclaimer over 6,184,226 was filed on October 5, 2001, thus this rejection has been rendered moot.

CONCLUSION

It is respectfully submitted that a *prima facie* case of lack of enablement has not been established. Further, the claims have been amended to overcome the indefiniteness rejection or definitions have been provided to show that the terms at issue would be readily understood by a skilled artisan. With regard to the art rejections, the claims have been amended to overcome the anticipation rejections and the references cited in the obviousness rejection cannot be cited properly against the present claims. A comparison of the claims associated with the statutory double patenting rejection show that this rejection was made in error. Finally, terminal

disclaimers have been previously filed on October 5, 2001 which address the obviousness type double patenting rejection.

Thus, this is respectfully submitted that the application is in condition for allowance and such action is respectfully requested. If there are outstanding matters that would prevent the present application from being allowed, the Examiner is kindly requested to telephone the undersigned to address such matters.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 219002028402.

Respectfully submitted,

Dated: May 22, 2003

By: _____

Carolyn A. Favorito
Registration No. 39,183

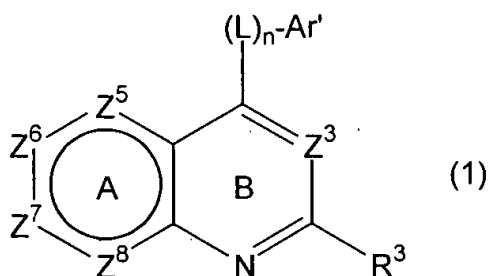
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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice Amended) A method to inhibit p38 α activity, which method comprises contacting said p38 α with a compound of the formula:



or the pharmaceutically acceptable salts thereof

wherein R³ comprises a substituted or unsubstituted aromatic moiety, wherein said aromatic moiety is a monocyclic or fused bicyclic moiety containing 5-12 ring member atoms, optionally comprising one or more heteroatoms selected from O, S and N;

wherein Z³ is N and each remaining Z is CR² or N, wherein no more than two Z positions in ring A are N, and wherein two adjacent Z positions in ring A cannot be N;

each R² is either

(i) independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyl, wherein each of alkyl, alkenyl, alkynyl and acyl may optionally contain 1-2 O, S or N, aryl, and arylalkyl, each of said aryl and arylalkyl optionally containing 1 or more O, S or N and wherein in each of the foregoing other than H may be unsubstituted or substituted with 1-3 substituents selected independently from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkylaryl, aroyl, N-aryl, NH-alkylaryl, NH-aroyl, halo, OR, NR₂, SR, -SOR, -SO₂R, -OCOR, -NRCOR, -NRCONR₂, -NRCOOR, -NRSOR, -NRSO₂R, -OCONR₂, RCO, -COOR, -SO₃R, -CONR₂, SO₂NR₂, CN, CF₃, and NO₂, wherein each R is independently H or alkyl (1-4C), and wherein any aryl or aroyl groups on said substituents may be further substituted by alkyl, alkenyl, alkynyl, halo, OR, NR₂, SR, -SOR, -SO₂R, -OCOR, -NRCOR, -NRCONR₂, -NRCOOR, -NRSOR, -NRSO₂R, -OCONR₂, RCO, -COOR, -SO₃R, -CONR₂, SO₂NR₂, CN, CF₃, and NO₂, wherein each R is independently H or alkyl (1-4C), or

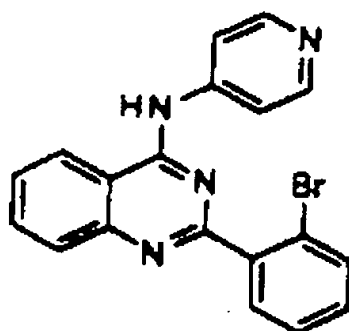
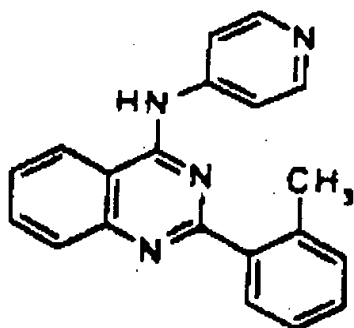
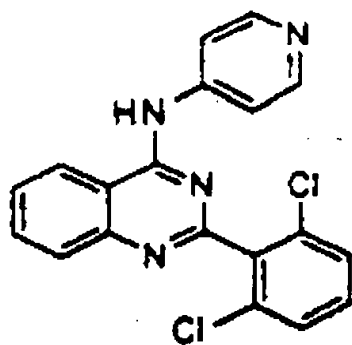
(ii) independently selected from the group consisting of halo, OR, NR₂, SR, -SOR, -SO₂R, -OCOR, -NRCOR, -NRCONR₂, -NRCOOR, NRSOR, NRSO₂R, -OCONR₂, RCO, -COOR, -SO₃R, NRSOR, NRSO₂R, -CONR₂, SO₂NR₂, CN, CF₃, and NO₂, wherein each R is independently H or alkyl (1-4C);

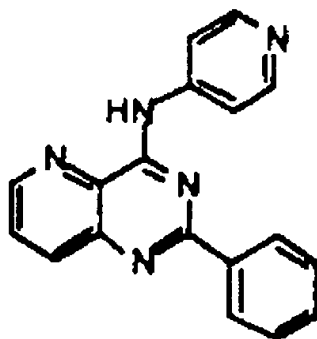
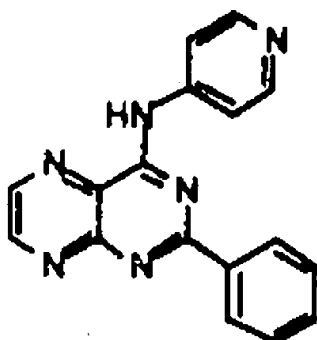
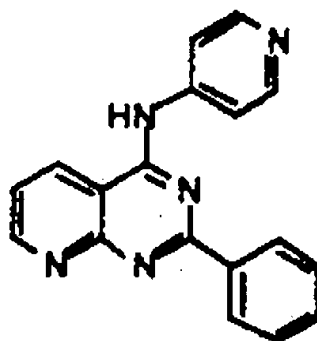
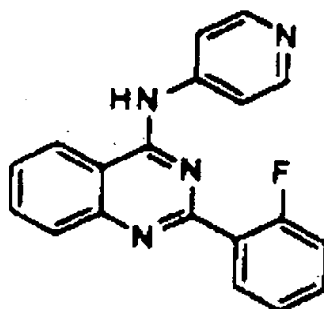
wherein L is a divalent moiety that provides a distance of 2-8Å between ring B and Ar';

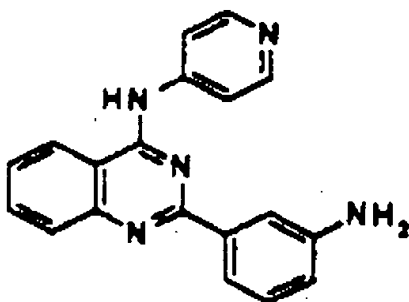
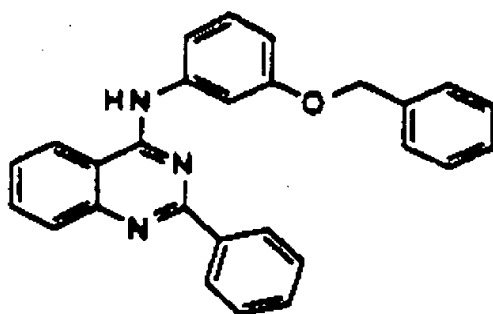
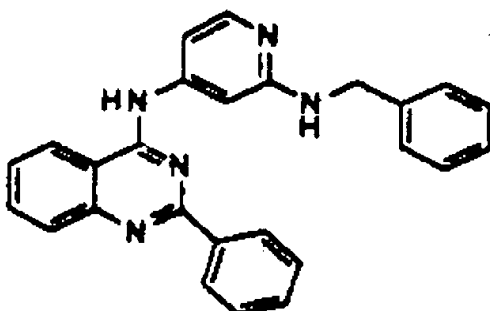
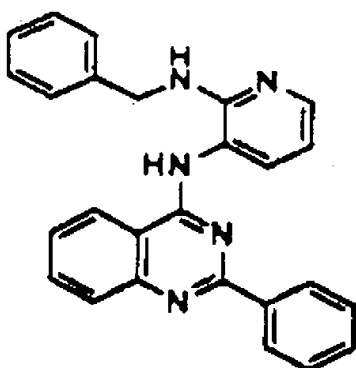
n is 0 or 1; and

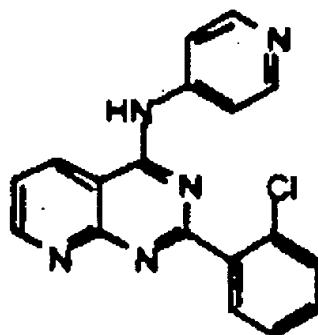
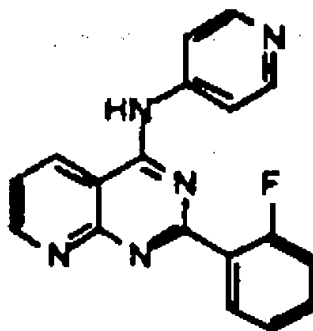
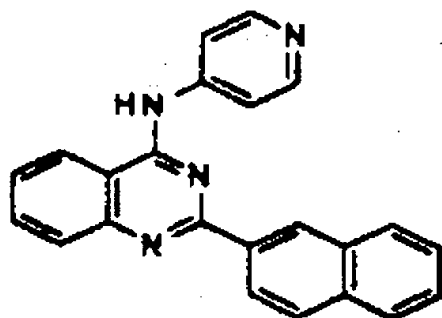
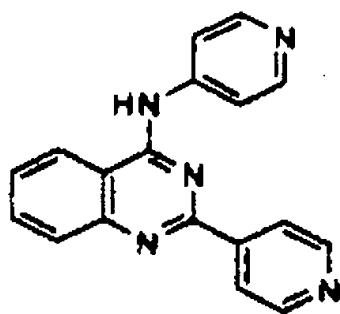
Ar' is a cyclic hydrocarbyl aliphatic, cyclic [heteroaliphatic] hydrocarbyl aliphatic containing one or more heteroatoms or a monocyclic or polycyclic aromatic moiety any of the foregoing optionally substituted with 1-3 substituents, wherein two of said substituents may form a 5-7 member cyclic optionally heterocyclic aliphatic ring and wherein Ar' and any said substituents thereon forming a cyclic aliphatic ring, may optionally contain one or more ring atoms selected from O, S and N, wherein said compound inhibits p38α activity.

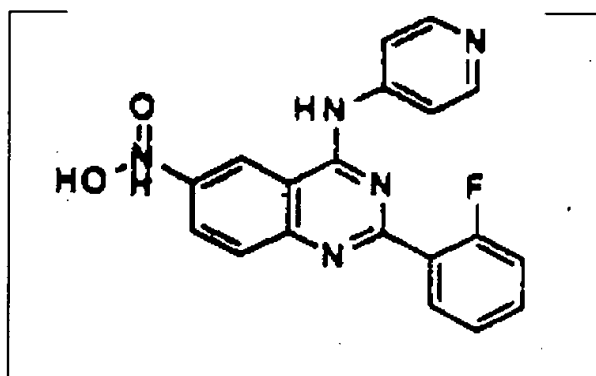
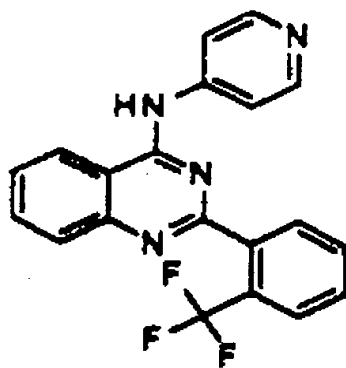
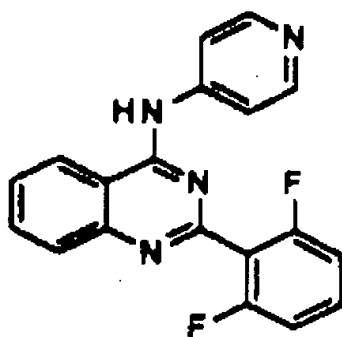
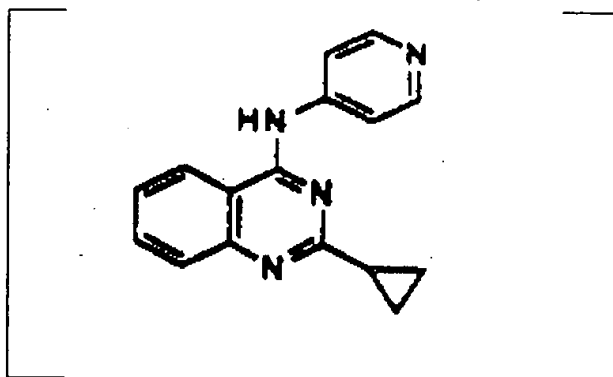
17. (Amended) The method of claim 1 wherein the compound of formula (1) is selected from the group consisting of the following compounds:

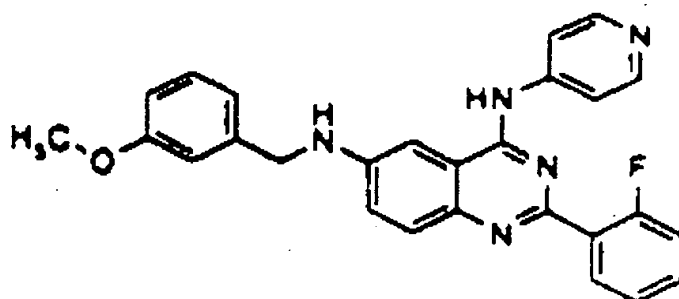
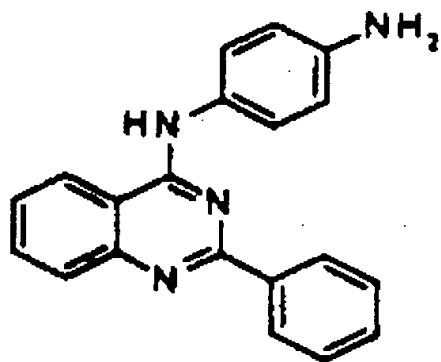
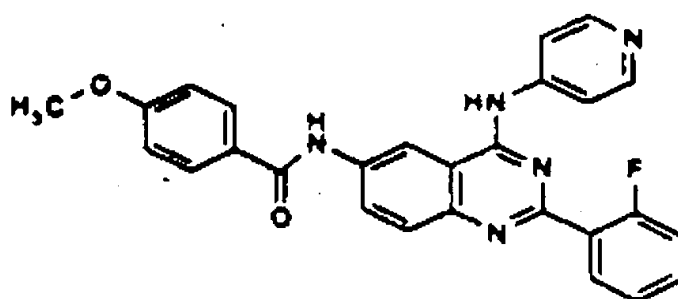
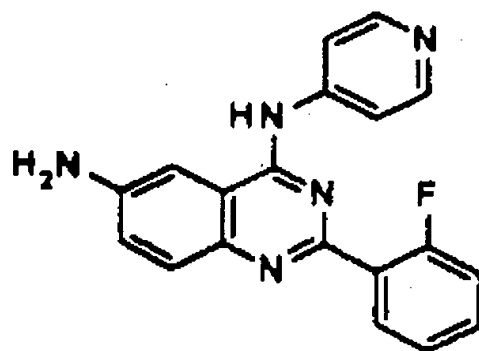


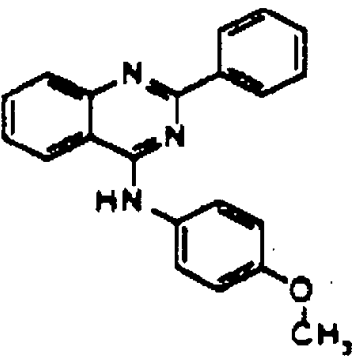
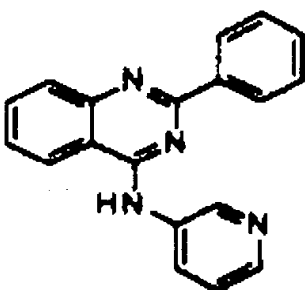
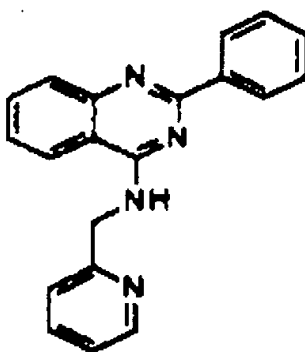
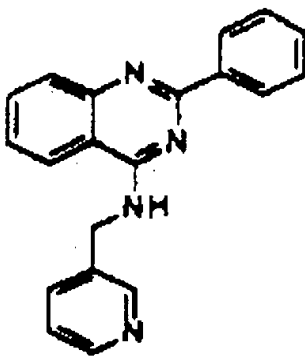


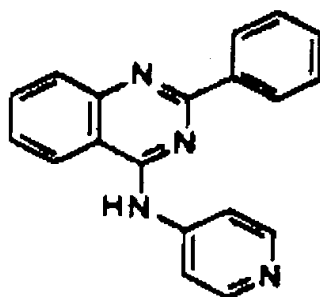
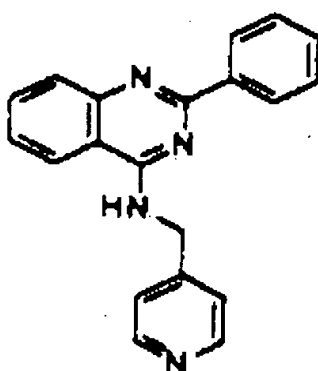
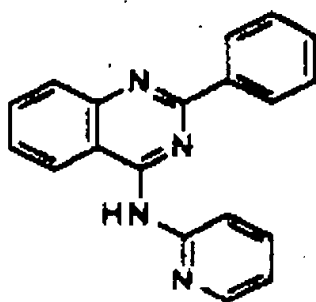


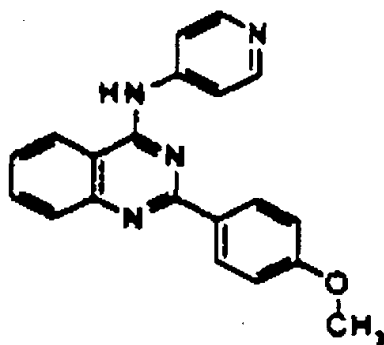
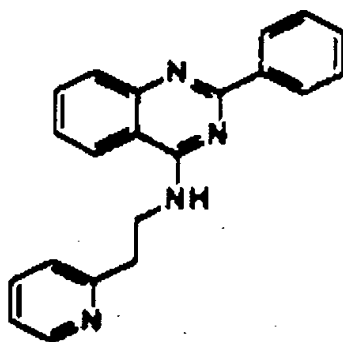
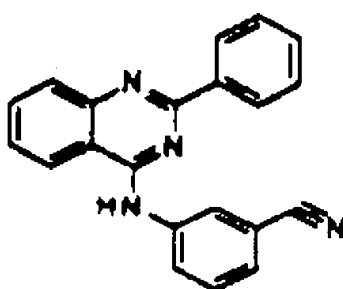
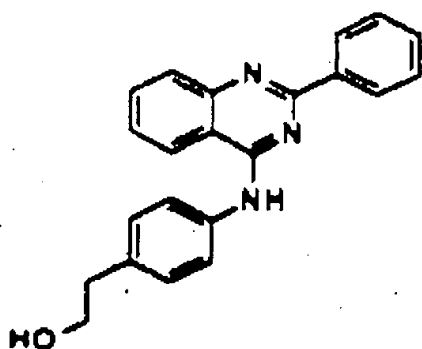


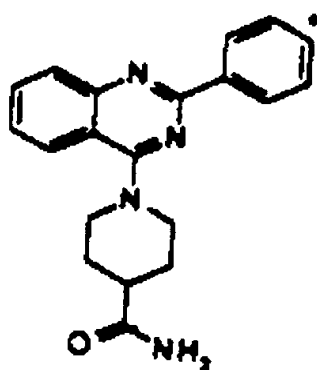
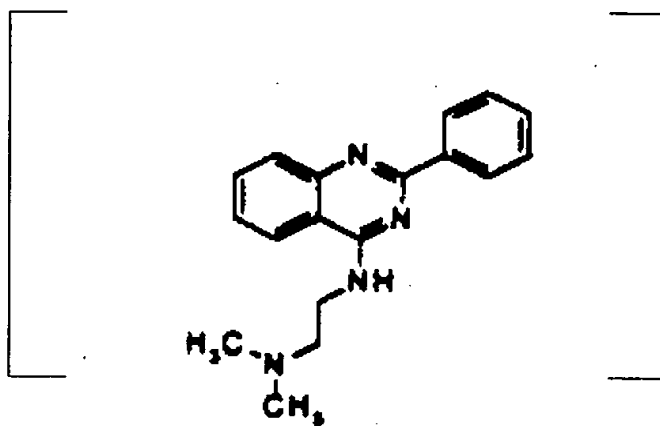
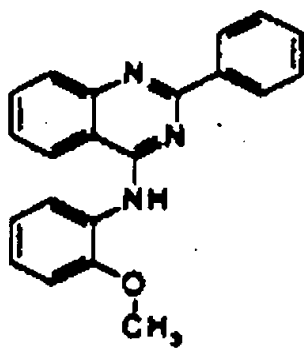


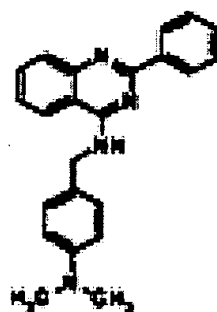
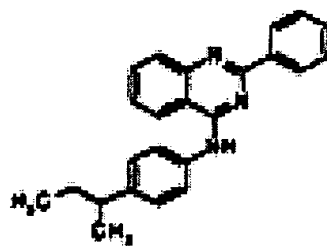
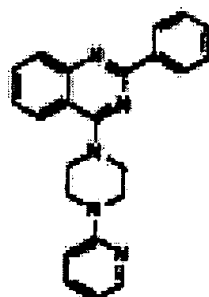
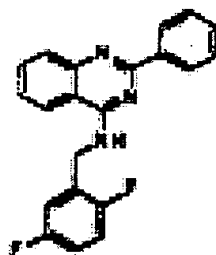


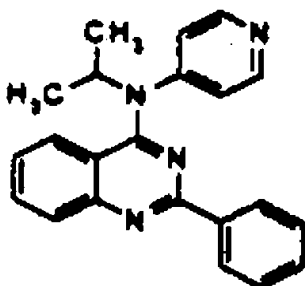
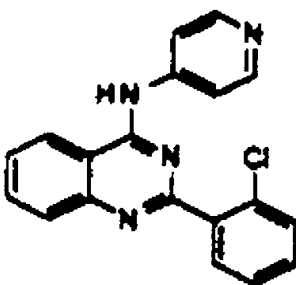
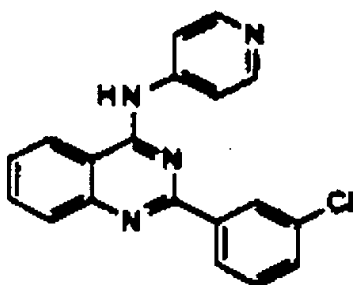
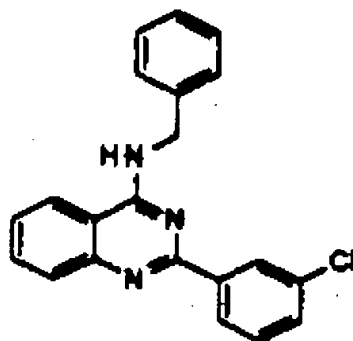


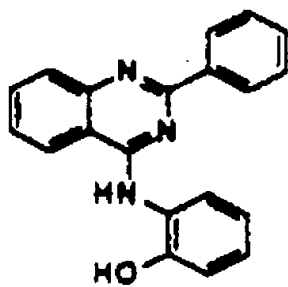
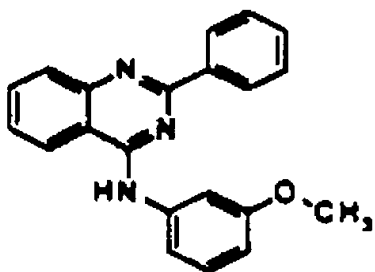
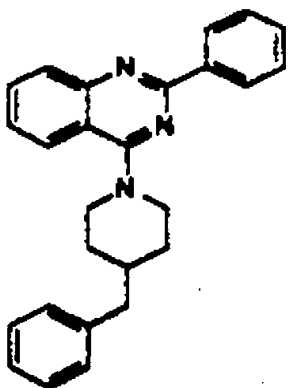
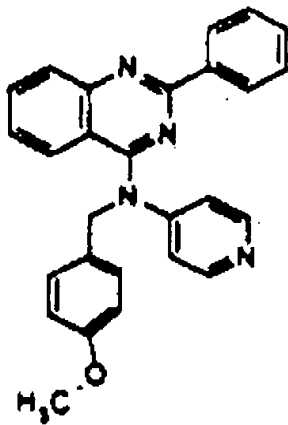


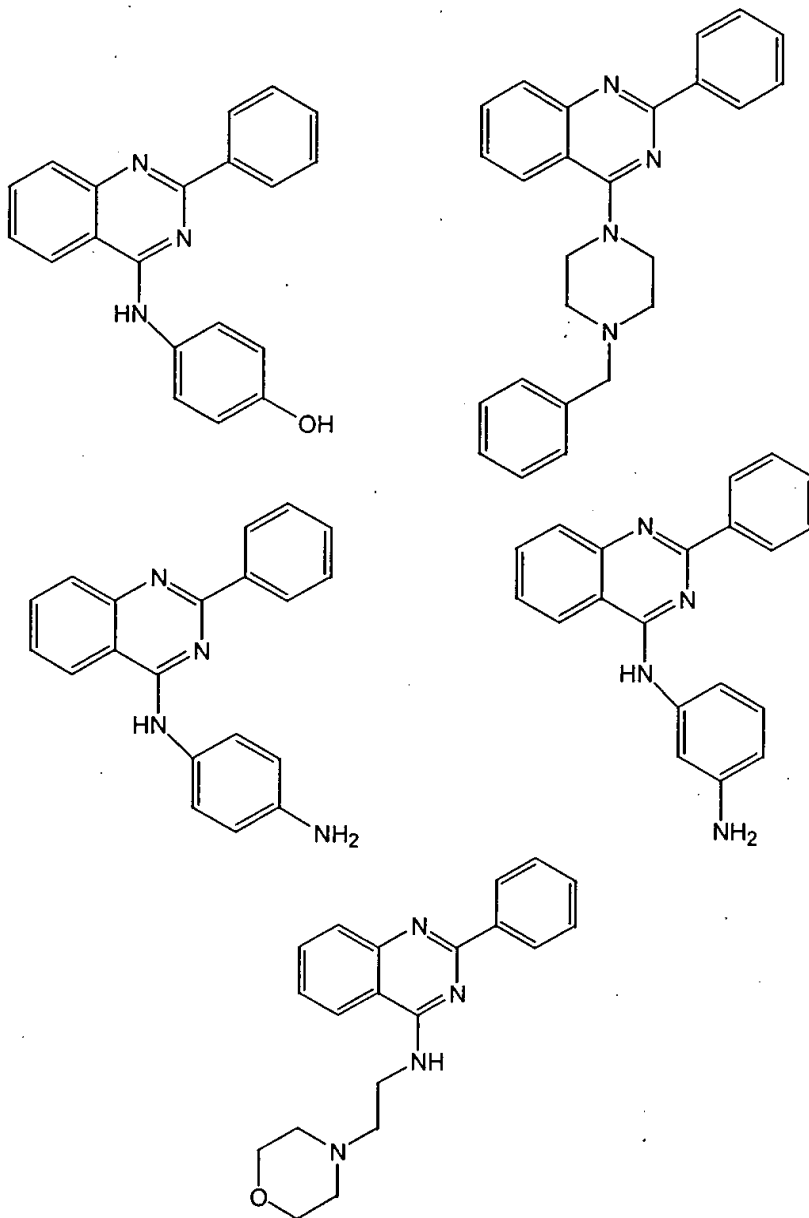


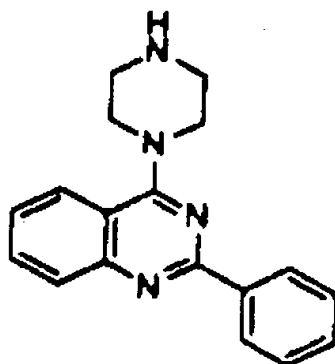
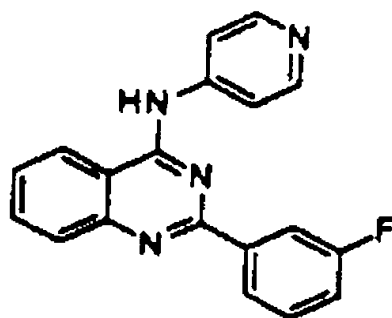
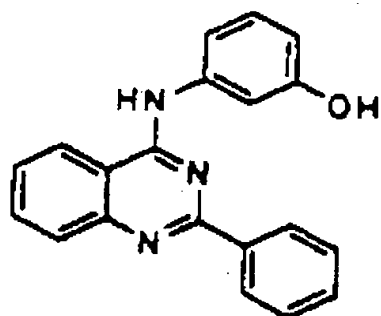


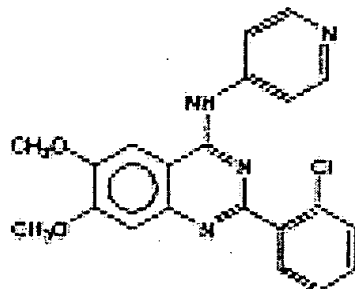
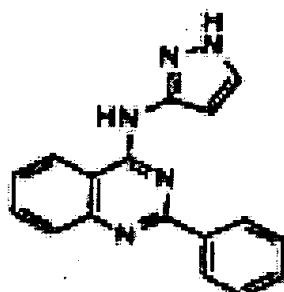
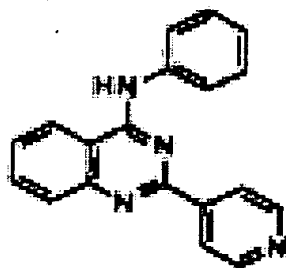


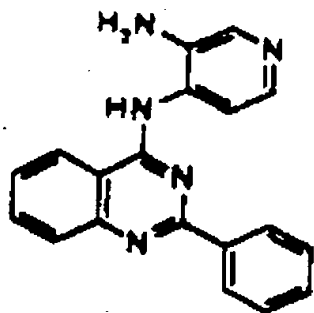
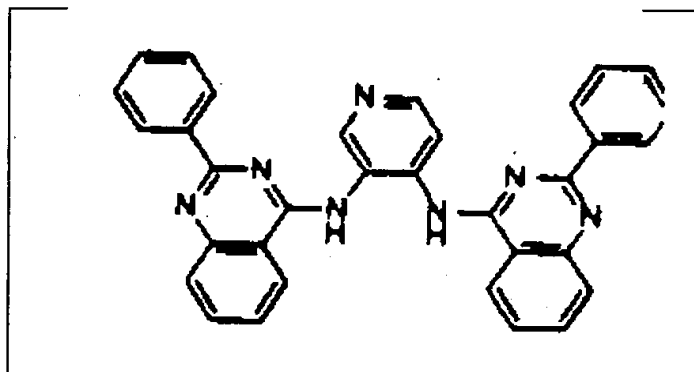
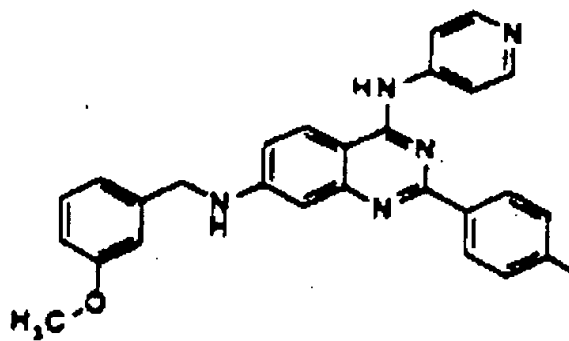
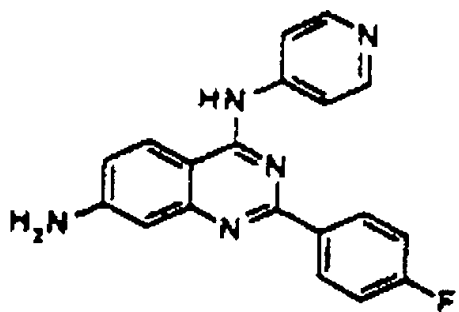


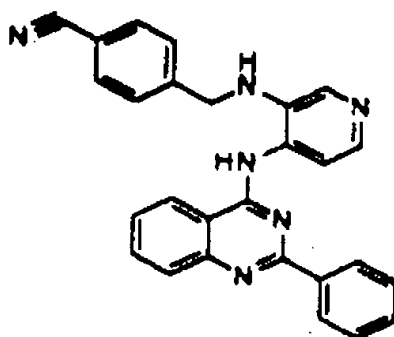
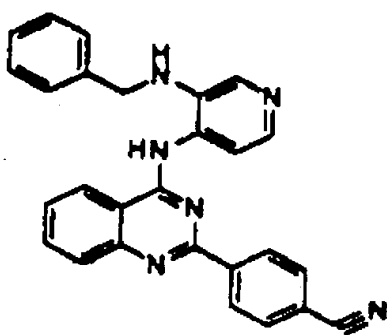
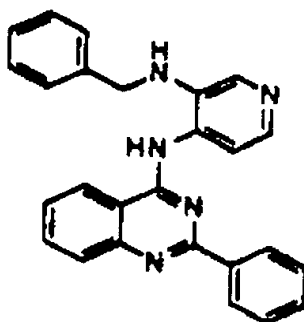
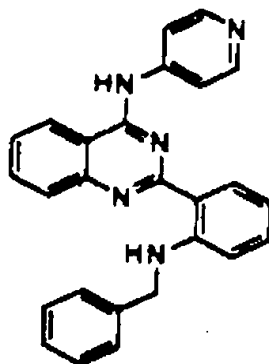


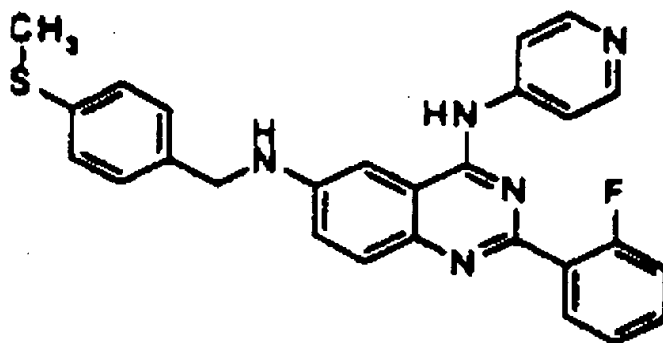
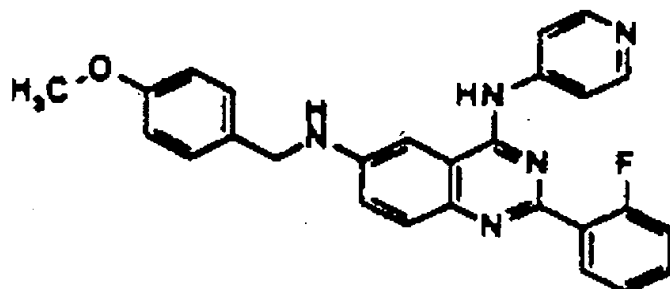
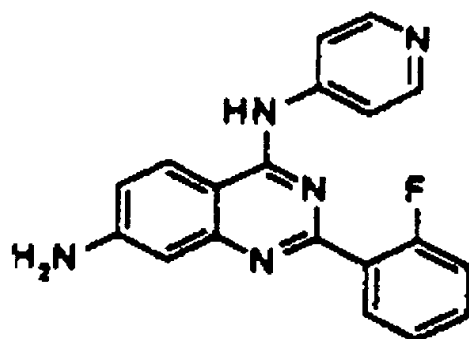
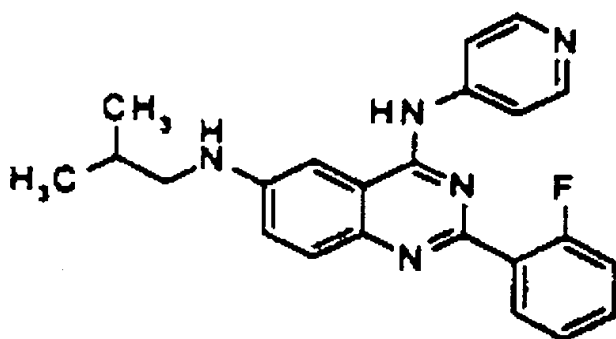


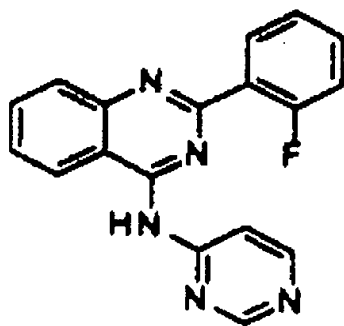
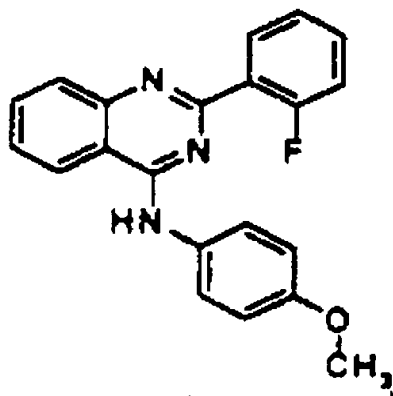
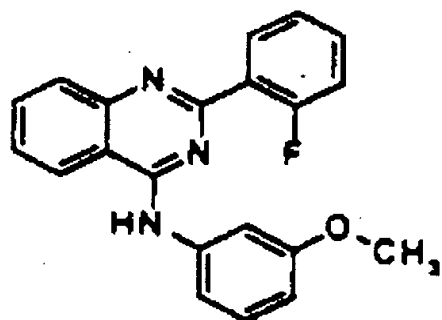


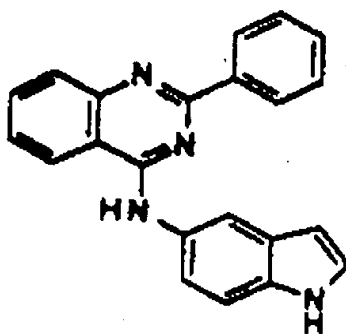
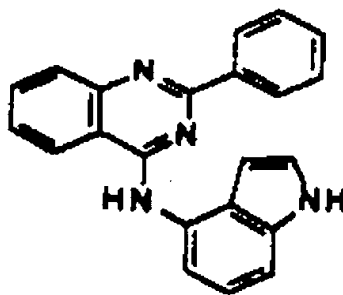
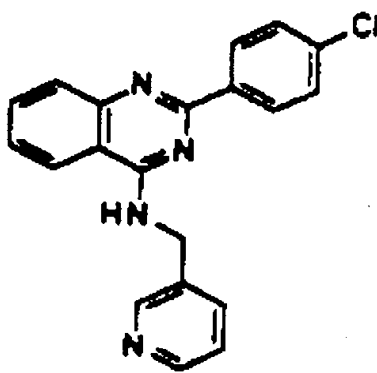
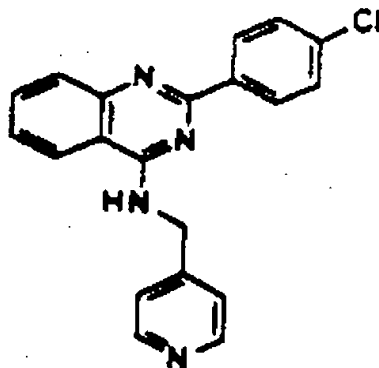


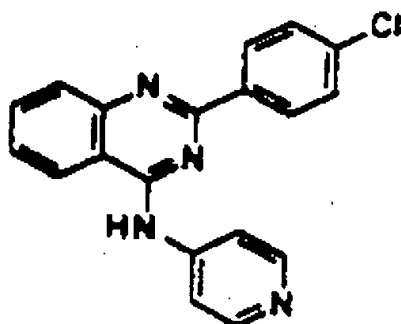
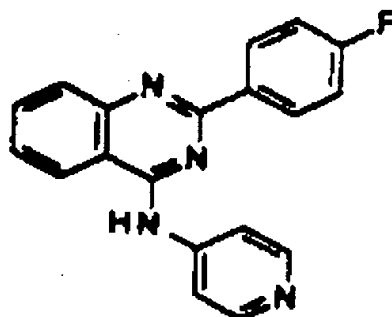
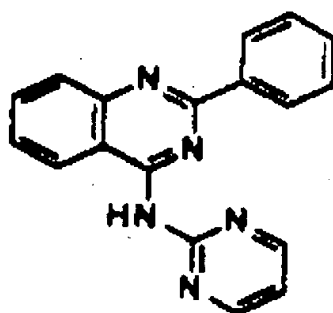
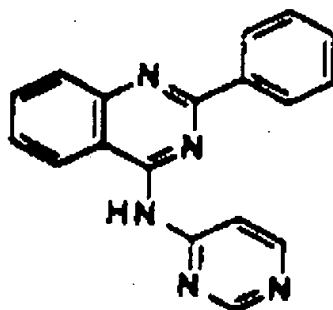












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Medical Dictionary

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Main Entry: **al·i·phat·ic**

Pronunciation: "al-&- 'fat-ik

Function: *adjective*

: of, relating to, or being an organic compound (as an alkane or alkene) having an open chain structure -- compare **ALICYCLIC**, **AROMATIC** 2

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Medical Dictionary

The latest word on medical terms

Main Entry: **al-i-cy-clic**

Pronunciation: "al-&-'sI-klik, -'sik-lik

Function: *adjective*

: of, relating to, or being an organic compound that contains a ring but is not aromatic
compare ALIPHATIC

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Medical Dictionary

The latest word on medical terms

Main Entry: **het·ero·at·om**

Pronunciation: 'het-&-rO-"at-&m

Function: *noun*

: an atom other than carbon in the ring of a heterocyclic compound

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